

Inventors: Border, Wayne A., et al.  
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Docket No. 066821-0236

**Remarks**

Claims 1-18 are pending. Claims 1, 2, 5-7, 10, and 13-15 as they read on methods of treating glomerulonephritis with anti-TGF-beta antibodies are under consideration in the instant application. Claims 3, 4, 8, 9, 11-12 and 16-18 have been withdrawn from consideration as being drawn to a non-elected inventions.

Claim 6 has been amended to delete the words "in antibodies." No new matter is introduced by the amendment and entry is respectfully requested.

**Regarding 35 U.S.C. §112, Second Paragraph**

The rejection of claims 6, 7 and 10 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention is respectfully traversed.

The Office Action asserts that claims 6-7 and 10 are indefinite in the recitation of "suppressing the activity of TGF-beta in antibodies because the recitation of "in antibodies" is allegedly nonsensical. Applicants submit that this rejection has been rendered moot by deletion of the phrase "in antibodies" from claim 6. Accordingly, Applicants respectfully request removal of the rejection of claims 6, 7 and 10 under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention.

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Regarding 35 U.S.C. §102

The rejection of claims 1, 2, 5-7, 10, and 13 and 15 under 35 U.S.C. §102(e) as allegedly anticipated by Dasch et al. (U.S. Patent No. 5,772 998) is respectfully traversed.

The Office Action asserts that Dasch et al. teach the use of TGF-beta-specific antibodies to neutralize the effects of TGF-beta in conditions including lung fibrosis, liver cirrhosis, fibrotic skin disorders and scarring. The Office Action further alleges that the claimed functional limitations would be inherent properties of the referenced methods to treat various fibrotic conditions with the same neutralizing TGF-beta-specific antibodies. The Examiner alleges that, although the reference is silent about decreasing the production of a proteoglycan by a cell wherein the proteoglycan is selected from the group consisting of biglycan and decorin, it does not appear that the claim language or limitations result in a manipulative difference in the method steps when compared to the prior art disclosure.

Applicants respectfully submit that the Examiner appears to disregard an important perquisite for making an inherency rejection, which is that the inherent feature must **necessarily** be present in the prior art:

Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.

*MEHL/Biophile Int'l Corp. v. Milgram*, 192 F.3d 1362, 1365, 52 USPQ2d 1303, 1305 (Fed. Cir. 1999)

To establish inherency, the evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill.

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*In re Oelrich*, 666 F.2d 578, 581-82 (C.C.P.A. 1981).

The Court of Appeals for the Federal Circuit analyzes inherent disclosures on the basis of requiring an inherency to be "**necessarily present**" and not merely sometimes, occasionally, or possibly present. At the patent prosecution stage, the United States Patent and Trademark Office similarly requires an examiner to supply an applicant either with a rationale for the inherent disclosure or evidence demonstrating the presence of the inherency. The Examiner is reminded that is not Applicants' burden to prove that claim elements not taught by the Dash patent are not necessarily present in the disclosure of Dash et al. The reference is silent about both the TGF-beta induced accumulation of extracellular matrix in a tissue as well as about decreasing the production of a proteoglycan by a cell.

Furthermore, the Patent Office has long acknowledged that the initial burden in establishing an inherency rejection rests with the Examiner, noting that:

in relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristics necessarily flow from the teaching of the applied art.

*Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990).

In view of the above, Applicants respectfully submit that the Examiner has not met the burden of providing a basis in fact to reasonably support the determination that the allegedly inherent characteristics necessarily flow from the Dasch et al. reference. Accordingly, Applicants respectfully request removal of the rejection of claims 1, 2, 5-7, 10, and 13-15 under 35 U.S.C. §102(e) as allegedly anticipated by Dasch et al. (U.S. Patent No. 5,772 998).

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Regarding 35 U.S.C. §103

The rejection of claims 1, 2, 5-7, 10, and 13-15 are rejected under 35 U.S.C. §103(a) as allegedly rendered obvious by Dasch et al. (U. S. Patent No. 5,772 998) in view of Ruoslahti et al. (U.S. Patent No. 5,583,103) and/or Bassols et al. (J. Biol. Chem. 263: 3039-3045, 1988) is respectfully traversed.

The Office Action concedes that Dasch et al. differs from the claimed methods by not disclosing that TGF-beta is responsible, at least in part, for glomerulonephritis. Ruoslahti et al. allegedly disclose that excessive accumulation of extracellular matrix in glomerulonephritis involves TGF-beta and that by treating TGF-beta regulated activities, one treats certain pathologies including fibrotic disease and glomerulonephritis. Further, Ruoslahti et al. are further alleged to disclose that TGF-beta specific antibodies were able to inhibit the activity of TGF-beta. Bassols et al. allegedly describe that TGF- regulates the expression of the extracellular matrix chondroitin/dermatan sulfate proteoglycans and proteoglycans in kidney and that TGF-beta induces kidney fibroblast proliferation. The Examiner concludes that, in the absence of evidence to the contrary, the above references render the invention as a whole *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Applicants respectfully disagree.

Applicants respectfully maintain that the Office has not met the burden the law allocates to it with regard to establishing a *prima facie* case of obviousness.

First, the prior art references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content.

Second, the prior art references upon which the Office relies to support the present rejection, when viewed in combination, do not provide the skilled person with a reasonable expectation of success to achieve the claimed invention.

The Dasch et al. '998 patent describes a method of neutralizing the inhibitory effects of TGF- $\beta$  and further references several species of pathologies, including interstitial lung fibrosis, liver cirrhosis, fibrotic skin disorders such as scleroderma and scarring. Far from containing a suggestion of the claimed method of decreasing the deleterious TGF- $\beta$  induced accumulation of extracellular matrix (ECM) associated with glomerulonephritis by contacting a tissue with an anti TGF  $\beta$  antibody that binds to TGF- $\beta$ , Dasch et al. does not even contain a reference to glomerulonephritis.

The secondary reference U.S. Patent No. 5,583,103, to Ruoslahti et al., is a continuation of application Ser. No. 07/467,888, filed on Jan. 22, 1990, subsequently abandoned, which is a continuation-in-part of application Ser. No. 07/212,702, filed Jun. 28, 1988. The priority document application Serial No. 07/212,702, which is the only document in the lineage that predates the priority date of the above-identified application, describes use of the proteoglycan decorin to treat cell proliferation and sets forth glomerulonephritis as a disease with a proliferative component. The only reference to TGF- $\beta$  in the '702 disclosure is a statement in the introductory paragraph of the background section that TGF- $\beta$  is a multifunctional factor that inhibits growth of some cell types, but can also stimulate cell proliferation. Significantly, Ruoslahti et al. does not teach or suggest the inhibition of TGF- $\beta$  activity for the purpose of decreasing the deleterious accumulation of the ECM or any of its components nor does it suggest that glomerulonephritis is associated with TGF- $\beta$  induced accumulation of extracellular matrix (ECM).

The secondary reference by Bassols et al., *J. Biol. Chem.* 263:3039-3045 (1988), does not teach or suggest the use of any agent, including anti-TGF- $\beta$  antibody, *in vivo* or in a tissue nor does the reference mention glomerulonephritis. Bassols et al. does not teach or suggest the inhibition of TGF- $\beta$  activity for the purpose of decreasing the deleterious accumulation of the ECM or any of its components nor does it suggest that glomerulonephritis is associated with TGF- $\beta$  induced accumulation of extracellular matrix (ECM).

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Taken together, the references upon which the Office relies to support the present rejection do not give rise to the requisite motivation to combine their content. Furthermore, the skilled person familiar with the cited references would not have had a reasonable expectation of success with regard to suppressing the deleterious accumulation of the TGF- $\beta$  induced extracellular matrix in a tissue by administering an agent which suppresses the extracellular matrix producing activity of TGF- $\beta$ . Accordingly, a *prima facie* case of obviousness has not been established and the rejection of claims 1, 2, 5-7, 10, and 13-15 as rendered obvious by the cited references is unsupported and should properly be withdrawn.

Regarding Obviousness-Type Double Patenting

Applicants acknowledge and defer responding to the provisional rejection of claims 1, 2, 5-7, 10, and 13-15 under the judicially created doctrine of obviousness-type double patenting over co-pending application Serial No. 08/349,479.

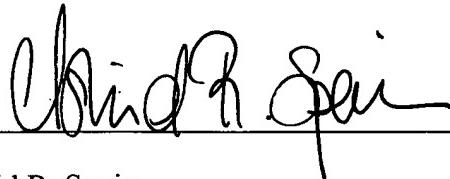
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**Conclusion**

In light of the Amendments and Remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to contact the undersigned attorney with any questions related to this application.

Respectfully submitted,



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